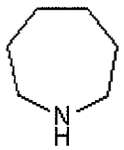
ROBUST SUMMARY

1.0 Substance Information

CAS Number: 111-49-9

Chemical Name: 1H-Azepine, hexahydro-

Structural Formula:



Other Names:
Azacycloheptane
1-Azacycloheptane
Azepine, hexahydro
Cyclohexamethylenimine
CP 18407
Cycloheptane, 1-aza
G 0
G 0 (amine)
Hexahydroazepine
Hexamethyleneimine
HMI
Homopiperidine
Perhydroazepine

Exposure Limits: None

2.0 Physical – Chemical Properties

2.1 Melting Point

Value:	-37°C
Decomposition:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p.574, John Wiley and Sons, Inc., New York.
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (1958). Unpublished Data.

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 732, Van Nostrand Reinhold Company, New York.

2.2 Boiling Point

Value:	138°C
Decomposition:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Lide, D. R. (ed.) (1998-1999). CRC Handbook of Chemistry and Physics, 79th ed., p. 3-16, CRC Press Inc., Boca Raton, FL.
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (1958). Unpublished Data.

Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 574, John Wiley and Sons, Inc., New York

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1939, John Wiley and Sons, Inc., New York.

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 732, Van Nostrand Reinhold Company, New York.

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom. Khim. Veschestv, 10:25-35.

2.3 Density

Value:	0.8799
Temperature:	20/4°C
Method:	No Data
GLP:	Unknown
Results:	No additional data.
Reference:	Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 574, John Wiley and Sons, Inc., New York.
Reliability:	Not assignable because limited study information was

available.

Additional References for Density:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (1958). Unpublished Data.

DuPont Co. (n.d.). Unpublished Data.

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1939, John Wiley and Sons, Inc., New York.

Lide, D. R. (ed.) (1998-1999). CRC Handbook of Chemistry and Physics, 79th ed., p. 3-16, CRC Press Inc., Boca Raton, FL.

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 732, Van Nostrand Reinhold Company, New York.

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom. Khim. Veschestv, 10:25-35.

2.4 Vapor Pressure

Value:	8.09 mm Hg
Temperature:	25°C
Decomposition:	No Data
Method:	Measured
GLP:	Unknown
Reference:	Daubert, T. E. and R. P. Danner (1989). Physical and Thermodynamic Properties of Pure Chemicals Data Compilation, Taylor and Francis, Washington, DC (HSDB/562; NISC/EF-0010375).
Reliability:	Not assignable because limited study information was available.

Additional References for Vapor Pressure:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

Lyman, W. J. (1985). In Environmental Exposure From Chemicals, Vol. I, Neely, W. B. and G. E. Blau (eds.), p. 31, CRC Press, Boca Raton, FL (HSDB/562).

2.5 Partition Coefficient (log K_{ow})

Value:	1.7
Temperature:	No Data
Method:	Estimated
GLP:	Not Applicable
Reference:	Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92 (HSDB/562).

Reliability: Estimated value based on accepted model.

Additional References for Partition Coefficient (log Kow): None Found.

2.6 Water Solubility

Value: 3.19×10^4 mg/L

Temperature: 25 °C
pH/pKa: No Data
Method: No Data
GLP: Unknown
Remark: EPA noted that the value given in this reference is the activity coefficient, which is unitless.
Reference: Yalkowsky, S. H. and R. M. Dannenfelser (1992). The AQUASOL Database of Aqueous Solubility, 5th ed., University of Arizona, College of Pharmacy, Tucson, AZ (HSDB/562).
Reliability: Not assignable because limited study information was available.

Value: 4.4×10^4 mg/L
Temperature: 25°C
pH/pKa: 10.82
Method: Modeled.

Solubility - WSKOWWIN v.1.40, module of EPIWIN v3.05 (Syracuse Research Corporation). Water solubility is estimated from log Kow using molecular weight and molecular fragment correction factors.

pKa – SPARC on-line calculator, University of Georgia.

GLP: Not Applicable
Reference: Solubility - Meylan, W. M. et al. (1996). Environ. Toxicol. Chem., 15:100-106. pKa - http://ibmlc2.chem.uga.edu/sparc/index.cfm
Reliability: Estimated values based on accepted models.

Additional References for Water Solubility:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (1958). Unpublished Data.

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1939, John Wiley and Sons, Inc., New York.

2.7. Flash Point

2.7.1 Flash Point

Value:	31.5 ^{o}C
Method:	Closed cup
GLP:	No
Remarks:	Data obtained on a >99% pure HMI sample.
Reference:	INVISTA S.á r.l internal test report (2008).
Reliability:	Reliable. Study was conducted in an ISO 9001 certified laboratory.

2.7.2 Flash Point

Value:	45 ± 2 ^{o}C
Method:	A9, 92/69/EEC; Closed Cup Equilibrium Method
Remarks:	On a crude HMI sample of unknown purity. 2 mL sample of test material allowed to equilibrate in tester sample cup at set temperature. Test flame introduced into cup for 2 seconds and observations made for ignition of vapor. Procedure repeated a number of times at increased temperatures to obtain final results.
GLP:	Yes
Reference:	INVISTA S.á r.l Internal Report (2006). SafePharm Laboratory study no. SPL 2231/0003.
Reliability:	Klimisch Code 1 – Reliable without Restriction; Study was conducted according to current test guidelines, followed GLPs, and was well documented.

2.7.3 Flash Point

Value:	99 ^{o}F (37.2 ^{o}C)
Method:	Open cup
GLP:	No
Reference:	U. S. Coast Guard, Department of Transportation (1978). CHRIS – Hazardous Chemical Data, Manual Two, U. S. Government Printing Office, Washington, DC (HSDB/562).
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (1958). Unpublished Data.

DuPont Company (n.d.). Unpublished Data.

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1939, John Wiley and Sons, Inc., New York.

2.8 Flammability

Results:	1.6 -2.3% in air
Method:	No Data
GLP:	No
Reference:	U. S. Coast Guard, Department of Transportation (1978). CHRIS – Hazardous Chemical Data, Manual Two, U. S. Government Printing Office, Washington, DC (HSDB/562).
Reliability:	Not assignable because limited study information was available.

Additional References for Flammability:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (n.d.). Unpublished Data.

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	No Data
Temperature:	No Data
Direct Photolysis:	No Data
Indirect Photolysis:	No Data
Breakdown Products:	No Data
Method:	According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere (Bidleman, 1988), hexamethyleneimine, which has a vapor pressure of 8.09 mm Hg at 25 ^{o}C (Daubert and Danner, 1989), is expected to exist solely as a vapor in the ambient atmosphere. Vapor-phase hexamethyleneimine is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals (SRC, n.d.). The half-life for this reaction in air is estimated to be 4.3 hours (SRC, n.d.), calculated from its rate constant of 9.0x10^{-11} cm /molecule-^{3} sec at 25^{o}C determined using a structure estimation method (Meylan and Howard, 1993).
GLP:	Not Applicable
Reference:	Bidleman, T. F. (1988). Environ. Sci. Technol., 22:361-367 (HSDB/562). Daubert, T. E. and R. P. Danner (1989). Physical and Thermodynamic Properties of Pure Chemicals Data Compilation, Taylor and Francis, Washington, DC.

Meylan, W. M. and P. H. Howard (1993). Chemosphere, 26:2293-2299 (HSDB/562).

SRC (Syracuse Research Corporation) (n.d.) (HSDB/562).

Reliability: Estimated value based on accepted model.

Additional References for Photodegradation: None Found.

3.2 Stability in Water

Concentration: No Data
Half-life: No Data
% Hydrolyzed: No Data
Method: Based on a classification scheme (Swann et al., 1983), an estimated K_{oc} value of 20 (Mackay et al., 1996) indicates that hexamethyleneimine is expected to have limited adsorption to suspended solids and sediment in water (SRC, n.d.). With a pKa of 11.07 (Perrin, 1965), hexamethyleneimine will exist almost entirely in the protonated form in aqueous environments, and is not expected to volatilize from water surfaces.
GLP: Not Applicable
Reference: Swann, R. L. et al. (1983). Res. Rev., 85:17-28 (HSDB/562).

Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 4-9, 15-1 to 15-29, American Chemical Society, Washington, DC (HSDB/562).

Cabani, S. et al. (1971). Trans Faraday Soc., 67:1933-1942 (HSDB/562).

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.

Perrin, D. D. (1965). Dissociation Constants of Organic Bases in Aqueous Solution, IUPAC Chem. Data Ser., p. 101, Butterworth, London (HSDB/562).

SRC (Syracuse Research Corporation) (n.d.) (HSDB/562).

Reliability: Estimated value based on accepted model.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity)

Media: Air, Water, Soil, Sediments
Distributions: Air: 0.514%
Water: 46.7 %
Soil: 52.7%

	Sediment: 0.11%
Adsorption Coefficient:	Not applicable
Desorption:	Not Applicable
Volatility:	Not Applicable
Method:	Calculated according to Mackay, Level III, Syracuse Research Corporation Epiwin Version 3.05. Emissions (1,000 kg/hr) to air, water, and soil compartments using EPA Model defaults. Data Used: Molecular Weight: 99.18 Henry's Law Constant: $6.1x10^{-6}$ atm-m^3 /mole (Cabani et al., 1971) Vapor Pressure: 8.09 mm Hg (Daubert and Danner, 1989) Log Kow: 1.7 (Meylan and Howard, 1995) Soil Koc: 20.5 (calc by model)
GLP:	Not Applicable
Reference:	Cabani, S. et al. (1971). Trans Faraday Soc., 67:1933-1942 (HSDB/562). Daubert, T. E. and R. P. Danner (1989). Physical and Thermodynamic Properties of Pure Chemicals Data Compilation, Taylor and Francis, Washington, DC. Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92 (HSDB/562). Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming approach was developed by Dr. Donald Mackay and co-workers which is detailed in: Mackay, D. (1991). Multimedia Environmental Models; The Fugacity Approach, pp. 67-183, Lewis Publishers, CRC Press. Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626. Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.
Reliability:	Estimated value based on accepted model.

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation

Value:	Maximum biodegradability of 1.19% by Day 28. Hexamethyleneimine was toxic to the microbial inoculum at the test concentration of 2 mg Active Substance/L.

Breakdown Products:	No Data
Method:	OECD Guideline 301D, Closed Bottle Test
GLP:	Yes
Reference:	DuPont Co. (2003). Unpublished Data, EMSE Report No. 41 -03, "Ready Biodegradability of Hexamethyleneimine using the Closed-Bottle Test (OECD 301D)" (September 10).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for Biodegradation:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Jones, H. R. (1971). Environmental Control in the Organic and Petrochemical Industries, Noyes Data Corporation (cited in Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 732, Van Nostrand Reinhold Company, New York).

Rothkopf, S. S. and R. J. Bartha (1984). J. Amer. Oil Chem. Soc., 61:977-980.

3.5 Bioconcentration

Value:	BCF = 3.9. This value suggests that the potential for bioconcentration in aquatic organisms is low.
Method:	Estimated according to a classification scheme (Franke et al., 1994), using an estimated log Kow of 1.7 (Meylan and Howard, 1995).
GLP:	Not Applicable
Reference:	Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92 (HSDB/562). Franke, C. et al. (1994). Chemosphere, 29:1501-1514 (HSDB/562).
Reliability:	Estimated value based on accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1. Acute Toxicity to Fish

Type:	**96-hour LC_{50}**
Species:	Rainbow trout, *Oncorhynchus mykiss*
Value:	LC_{50} > 100 mg/L NOEC = 100 mg/L

Method:	OECD 203; Flow-Through Young rainbow trout fingerlings (6.2±0.2 cm) obtained from commercial hatchery; seven (7) fish per group, were used in a Limit Test at zero (untreated control) and 100 mg/L test article (regulatory limit for toxicity classification). Fish were housed in 22 L all-glass vessels with a loading factor of 0.21 g fish/L/day. Stock solutions were prepared daily in Milli-Q water, pH adjusted with 37% HCL, then added to a mixing flask with constant stirring (15 min) before final solutions were prepared via computerized dilution process. Endpoints measured in final study: death and clinical effects at approximately 3-, 24-, 48-, 72- and 96-hr. Daily AM and PM observations were also made for deaths. The pH and dissolved oxygen were recorded at the beginning and periodically during the study and water temperature was monitored continuously.
GLP:	Yes
Test Substance:	Hexamethyleneimine; purity 99.6%
Results:	Preliminary range-find toxicity study indicated LC50 >100 mg/L. NOEC = 100 mg/L (highest dosage tested). No clinical effects or deaths observed in treated group. Due to low analytical levels of the initial exposure concentration, fish were held an additional 24-h without food prior to study start. As no deaths occurred in this study, there was no negative impact on the results. Analytical variability among replicate samples of the exposure solutions was observed during the exposure period. However, based on recovery samples taken during the exposure period, actual test concentrations reached or even exceeded the 100 mg/L target concentration and thus supports the report conclusions. No loss was observed due to degradation of test material during the test period. All water quality parameters were considered within acceptable ranges and did not alter results of the study: O_2 > 6.0; water temp. = 16.3-16.9 ^{o}C; water hardness = 180 mg/L as $CaCO_3$; photoperiod = 16h; pH = 7.7± 0.3.
Reference:	INVISTA S.á r.l. l Internal Study (2006). NOTOX B.V. Study No.456749.
Reliability:	High; Study conducted according to current testing guidelines, followed GLPs, and is well documented. Klimisch Code = 1; Reliable without restriction

Additional References for Acute Toxicity to Fish: None Found.

4.2. Acute Toxicity to Invertebrates

4.2.1 Acute Toxicity to Invertebrates

Type:	**48 -hour EC_{50}**
Species:	Water flea, *Daphnia magna*
Value:	EC_{50} > 100 mg/L.(Measured); NOEC = 32 mg/L.
Method:	OECD Method 202; Flow-through >24 h old *D. magna* obtained from in-house colony; study was run in quadruplicate for each test solution. Animals housed in 1.5L stainless steel vessels. Stock solutions were prepared daily in Milli-Q water, pH adjusted with 37% HCL, then added to mixing flask with constant stirring (15 min) before final solutions were prepared via computerized dilution process. Endpoints measured in final study: immobilization at 24-h and 48-h, pH and dissolved oxygen at beginning and end of study and water temperature monitored continuously. Five (5) test concentrations plus an untreated control group were evaluated. Twenty (20) daphnids were used per concentration, 5 per replicate, with 4 replicates at each concentration.
GLP:	Yes
Test Substance:	Hexamethyleneimine; purity of 99.6% Results: Preliminary range-find toxicity study indicated an EC_{50} >10 <100 mg/L. Incidence (48-h) of immobilization in full study: Dose-mg/L. (% immobilized): 0 (0%), 10 (10%), 18 (10%), 32(5%), 56 (25%), and 100 (20%) An incidence of 10% immobilization was considered by the study director to be unrelated to treatment, based on laboratory historical data. Analytically determined test concentrations were 94-108% of nominal; thus final values are reported as target concentrations; no loss was observed due to degradation of test material during the test period. All water quality parameters were considered within acceptable ranges and did not alter results of the study: O_2 > 8.6; water temp. = $20^oC \pm 2$; water hardness = 250 mg/L as $CaCO_3$; photoperiod = 16h; pH = 8.0± 0.2.
Reference:	INVISTA S.á r.l. Internal Report (2006). NOTOX B.V. Study no. 456751.
Reliability:	High; Study conducted according to current testing guidelines, followed GLPs, and is well documented. Klimisch Code = 1; Reliable without restriction.

Additional References for Acute Toxicity to Invertebrates: None Found.

4.3. Acute Toxicity to Aquatic Plants

4.3.1 Acute Toxicity to Aquatic Plants

Type:	**72 -hour EC_{50}**
Species:	Green algae, *Selenastrum capricornutum*
Value:	E_BC_{50} (95% CI) = 43 (30-60) mg/L (Biomass) E_RC_{50} (95% CI) = 88 (58-120) mg/L (Growth) NOEC (Biomass) = 10 mg/L NOEC (Growth) = 10 mg/L
Method:	OECD TG Method 201 Freshwater algae from an in-house culture were used at a final concentration of 10^4 cells/ml. Algae were housed in 100 mL all-glass vessels with 50 mL test solution. Stock solutions were prepared daily in Milli-Q water, pH adjusted with HCL, then added to mixing flask with constant stirring (15 min) before final solutions were prepared. Three replicates of each test substance concentration and 6 replicates of untreated control solutions were used and incubated throughout the test period with continuous shaking. Cultures were grown under continuous light with intensity range of 80-99 $\mu E/m^2/s$. Test solutions were analyzed at the start and end of the exposure period. Endpoints measured included cell growth inhibition (biomass) and growth rate reduction (growth); measurements completed using a Cary 50 single-beam spectrophotometer. The pH was recorded at the beginning and end of the study, and water temperature monitored continuously. Test solutions were continuously aerated. Statistical calculations were based on OECD guidance (1984); modified according to S. Pack (1993).
GLP:	Yes
Test Substance:	Hexamethyleneimine; purity of 99.6%
Results:	Preliminary range-find toxicity study indicated expected EC_{50} values between 10-100 mg/L. Full Study: Analytical measurement confirmed accuracy of dose levels at study start (83-101%). No loss was observed due to degradation of test material during the test period. All water quality parameters were considered within acceptable ranges and did not alter results of the study: water temp. = 23±2 ^oC; water hardness = 24 mg/L as $CaCO_3$; pH = 8.1-8.2 at study start; 8.2-10.5 at study end. Five lowest concentrations exceeded preferred ceiling pH level (9.0) which apparently was related to a high rate of algal growth at these levels. This deviation had no effect on the conclusions of the report. Under the conditions of the

	study, the test substance reduced total cell growth and growth rate at 22 mg/L and higher.
Reference:	INVISTA S.á r.l.. Internal Report. (2006). NOTOX B.V. Study No. 456762.
Reliability:	High; Study conducted according to current testing guidelines, followed GLPs, and is well documented. Klimisch Code = 1; Reliable without restriction.

Additional References for Acute Toxicity to Aquatic Plants: None Found.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type:	**Oral ALD**
Species/Strain:	Male rats/ChR-CD
Value:	1000 mg/kg
Method:	The test substance, as an aqueous solution, was administered by intragastric intubation to male rats in single doses of 300, 450, 670, 1000, 1500, 2250, or 3400 mg/kg. Survivors were sacrificed after 14 days.
GLP:	No
Test Substance:	Hexamethyleneimine, purity 98.18%
Results:	Mortality occurred at ≥ 1000 mg/kg from 1 ¾ to 2 ¼ hours after dosing. Clinical signs observed at lethal doses included belly-to-cage posture, half-closed eyes, pallor, tremors, and convulsions. Clinical signs observed at non-lethal doses included belly-to-cage posture, half-closed eyes, and pallor on the day of dosing (≥ 450 mg/kg); bloody mouth-nose area for 1-2 days after dosing (≥ 450 mg/kg); weight loss for 2 -5 days (300 and 670 mg/kg); and diarrhea and continuous weight loss (450 mg/kg).
Reference:	DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 328-74.
Reliability:	High because a scientifically defensible or guideline method was used.

Type:	**Oral LD_{50}**
Species/Strain:	Rats/CRCD
Value:	50-500 mg/kg
Method:	Male rats (6/dose level) were orally intubated with 0, 50, or 500 mg/kg hexamethyleneimine. The rats were fasted overnight, prior to administration of the test material. Body weights and clinical signs were recorded, and all rats were necropsied.
GLP:	Yes
Test Substance:	Hexamethyleneimine (neat material), purity not specified
Results:	Mortality was 0/6, 0/6, and 6/6 at 0, 50, and 500 mg/kg, respectively. Mortality occurred on the day of dosing. Clinical signs of toxicity in the control rats, observed on the

	day of dosing, included brown-stained anogenital area (2/6) and diarrhea (1/6). No clinical signs of toxicity were observed in rats dosed with 50 mg/kg. Clinical signs of toxicity observed at 500 mg/kg included passiveness (6/6), prostration (2/6), ataxia (6/6), tremors (3/6), convulsions (2/6), salivation (6/6), abdominal breathing (3/6), brown-stained anogenital area (1/6), ptosis (6/6), and cyanosis (2/6). No macroscopic changes were observed in rats dosed at 0 or 50 mg/kg. Necropsy observations noted at 500 mg/kg included red-stained eyes (2/6), wet matted fur on the muzzle (6/6), whitened lungs (5/6), severely reddened stomach mucosa and intestines (6/6), and red fluid-filled stomach and intestines (6/6).
Reference:	Rohm and Haas (1985). Report No. 85R 0051 (cited in TSCA fiche OTS0540608).
Reliability:	Medium because a suboptimal study design was used.

Type:	**Oral LD_{50}**
Species/Strain:	Male and female rats/Sprague Dawley
Value:	9.6 mg/kg (lower and upper limits, 8.0-11.4 mg/kg)
Method:	Male and female rats (5 rats/dose level) were orally intubated with single doses of 3.98, 6.31, 10.0, or 15.8 mg/kg of the test substance. Observations were made for toxic signs. Surviving rats were sacrificed 14 days after dosing, and the viscera of the test rats were examined macroscopically. The LD_{50} was calculated according to the method of E. J. de Beer.
GLP:	No
Test Substance:	Hexamethyleneimine (HMI Refined), purity not specified
Results:	Mortality was 0/5, 2/5, 3/5, and 5/5 at 3.98, 6.31, 10.0, and 15.8 mg/kg, respectively. Survival time was 3-8 days. Toxic signs included reduced appetite and activity (5-10 days in survivors), gradually increasing weakness, collapse, and death. At autopsy there was lung hyperemia, slight liver discoloration, and acute gastrointestinal inflammation. Macroscopic examination revealed slight liver discoloration in some cases.
Reference:	Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-31, "Toxicological Investigation of CP 18407 – HMI Refined" (April 2) (cited in TSCA fiche OTS0539976).
Reliability:	Medium because a suboptimal study design was used.

Additional References for Acute Oral Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (n.d.). Unpublished Data.

DuPont Co. (1958). Unpublished Data, Haskell Laboratory Report No. 65-58.

DuPont Co. (1958). Unpublished Data.

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 330-74.

Monsanto Chemical Co. (1972). Younger Laboratories, Inc. Project Number Y-72-114, "Toxicological Investigation of HMI Binary Solution" (June 2) (cited in TSCA fiche OTS0534842).

Monsanto Chemical Co. (1973). Letter from P. L. Wright to N. J. Hunt (April 4) (also cited in OTS0571679).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-33, "Toxicological Investigation of CP 61337 – HMI Azeotrope" (April 2) (cited in TSCA fiche OTS0534827).

Izmerov, N. F. et al (1982). Toxicometric Parameters of Industrial Toxic Chemical Under Single Exposure, Centre of International Projects, GKNT, Moscow.

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom. Khim. Veschestv, 10:25-35 (CA71:47804w).

Zaeva, G. N. et al. (1974). Gig. Tr. Prof. Zabol., (2):29-32 (HEEP/75/02464; also cited in Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., John Wiley & Sons, Inc., New York).

Bazarova, L. A. and N. I. Osipenko (1967). Toksikol. Novykh Prom. Khim. Veshchestv, 9:91-101 (CA70:27261t).

Type:	**Inhalation ALC**
Species/Strain:	Male rats/ChR-CD
Exposure Time:	4 hours
Value:	2.45 mg/L (605 ppm)
Method:	Male rats were exposed to hexamethyleneimine at concentrations of 0.52, 1.32, 1.95, 2.45, 2.77, or 3.12 mg/L for 4 hours. The test substance was delivered at a constant rate into a round bottom flask heated to approximately 96 ^{o}C. Air metered into the flask carried the test vapors into a 20-liter exposure chamber usually containing 6 male rats (the 0.52 mg/L group contained 10 rats) weighing between 200 and 300 grams each. Exposures were for 4 hours, during which samples of the chamber atmosphere were analyzed for hexamethyleneimine by gas chromatography. The test rats were observed and weight records maintained for 14 days post-exposure, unless sacrificed for pathologic examination. Males exposed to 1.32 mg/L (2 at 1, 4, and 7 days

	post-exposure), 2.45 mg/L (2 at 14 days post-exposure), and 2.77 mg/L (2 upon death) were examined for pathologic alterations. At necropsy, 20 tissues from each rat were examined grossly and preserved in Bouin's fixative. The tissues were embedded in paraffin, sectioned, stained, and given a histopathologic examination.
GLP:	No
Test Substance:	Hexamethyleneimine, purity 98%
Results:	Mortality was 0/10, 0/6, 0/6, 1/6, 3/6, and 6/6 at 0.52, 1.32, 1.95, 2.45, 2.77, and 3.12 mg/L, respectively. Clinical signs included chewing and grooming motions (0.52, 1.32, and 1.95 mg/L), labored breathing (1.32, 1.95, 2.45, and 2.77 mg/L), gasping (2.45 mg/L), redness around the eyes and nose (2.45 mg/L), fasciculation (2.77 and 3.12 mg/L), and convulsions (2.77 mg/L). Post-exposure observations included weight loss (≤ 2.77 mg/L), lung congestion (1.95, 2.45, and 2.77 mg/L), corneal opacity (1.95, 2.45, and 2.77 mg/L), nasal discharge (2.45 and 2.77 mg/L), and lacrimation (2.77 mg/L). A mild total body cyanosis was observed in both rats at 2.77 mg/L that died during exposure, while subpleural white plaques, red focal spots, and congestion of the lungs were similar to the gross observations made in all test rats exposed similar to the gross observations made in all test rats exposed to 1.32 and 2.45 mg/L. Organs showing possible test substance-related effects included the lungs, trachea, and eyes. However, the histopathologic effects were difficult to interpret in the absence of a concurrent control group.
Reference:	DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 495-74 (also cited in TSCA fiche OTS0546547).
Reliability:	High because a scientifically defensible or guideline method was used. (Histologic examination is not generally part of this test design, hence no control rats were used.)

Additional References for Acute Inhalation Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1958). Unpublished Data, Haskell Laboratory Report No. 65-58.

Izmerov, N F. et al (1982). Toxicometric Parameters of Industrial Toxic Chemical Under Single Exposure, Centre of International Projects, GKNT, Moscow.

Monsanto Chemical Co. (1972). Younger Laboratories, Inc. Project Number Y-72-114, "Toxicological Investigation of: HMI Binary Solution" (June 2) (cited in TSCA fiche OTS0534842).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-31, "Toxicological Investigation of CP 18407 – HMI Refined" (April 2) (cited in TSCA fiche OTS0539976).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-33, "Toxicological Investigation of CP 61337 – HMI Azeotrope" (April 2) (cited in TSCA fiche OTS0534827).

Monsanto Chemical Co. (1973). Letter from P. L. Wright to N. J. Hunt (April 4) (also cited in OTS0571679).

Zaeva, G. N. et al. (1968). Aktual. Vop. Gig. Tr. Prof. Patol., Mater. Konf., 1st Meeting Date 1967, pp. 51-53 (CA72:53301).

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom. Khim. Veschestv, 10:25-35 (CA71:47804w).

Bazarova, L. A. and N. I. Osipenko (1967). Toksikol. Novykh Prom. Khim. Veshchestv, 9:91-101 (CA70:27261).

Data from this additional source were not summarized because the study design was not adequate. The focus of the study was to determine if the test substance was a Class B poison.

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 329-74.

Data from this additional source were not summarized because insufficient study information was available.

U. S. Coast Guard, Department of Transportation (1978). CHRIS – Hazardous Chemical Data, Manual Two, U. S. Government Printing Office, Washington, DC (HSDB/562).

Type:	**Dermal MLD (Minimal Lethal Dose)**
Species/Strain:	Male and female rabbits/New Zealand White
Value:	1260 - 2000 mg/kg
Exposure Time:	24 hours
Method:	The undiluted test substance was applied in increasing doses at increments of various fractional log intervals to the closely clipped, intact skin of male and female rabbits. The treated areas were covered with plastic strips, and the rabbits were held in wooden stocks for periods up to 24 hours. Observations were made for toxic signs, and the viscera of the test rabbits were examined macroscopically.
GLP:	No
Test Substance:	Hexamethyleneimine (HMI refined), purity not specified
Results:	The minimal lethal dose for male and female rabbits was 1260 - 2000 mg/kg. The compound was classed as mildly toxic by skin absorption in male and female rabbits.
Reference:	Monsanto Chemical Co. (1973). Younger Laboratories, Inc.

	Project Number Y-73-31, "Toxicological Investigation of CP 18407 – HMI Refined" (April 2) (cited in TSCA fiche OTS0539976).
Reliability:	Medium because a suboptimal study design was used.

Type:	**Dermal LD_{50}**
Species/Strain:	Rabbits/New Zealand White
Exposure Time:	24 -hours
Method:	Hexamethyleneimine (200 mg/kg neat material) was held under an impervious cuff in a continuous 24-hour contact with the intact skin of rabbits, from which the hair had been closely clipped. After the 24-hour exposure, the cuffs were removed and the application sites were wiped gently to remove the test substance. Body weights, clinical signs, and skin reaction were recorded, and necropsy was performed on all rabbits after 14 days.
GLP:	Unknown
Test Substance:	Hexamethyleneimine (neat material), purity not specified
Results:	One rabbit died 8-14 days after dosing. Severe erythema with blanching, and severe edema with pocketing were observed on Day 1. The skin irritation score was not evaluated after Day 1, since the pH of the test substance was found to be greater than 12. This test substance was classified as corrosive according to OECD guidelines. Only 1 rabbit exhibited clinical signs of toxicity, which included passiveness, ataxia, abdominal breathing, scant droppings, brown-stained anogenital area, mucous on dropsheet, and distended abdomen. The gross necropsy signs and cause of death were attributed to mucoid enteropathy, and were judged not to be related to treatment with the test-substance. No other clinical signs of toxicity were observed. Eschar at the application site was observed in all surviving rabbits at necropsy. Based on this range finding LD_{50}, the test material is not more than moderately toxic to male rabbits by a single dermal application.
Reference:	Rohm and Haas (1985). Report No. 85R 0051 (cited in TSCA fiche OTS0540608).
Reliability:	Medium because a suboptimal study design was used.

Additional References for Acute Dermal Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Monsanto Chemical Co. (1972). Younger Laboratories, Inc. Project Number Y-72-114, "Toxicological Investigation of HMI Binary Solution" (June 2) (cited in TSCA fiche OTS0534842).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-33, "Toxicological Investigation of CP 61337 – HMI Azeotrope" (April 2) (cited in TSCA fiche OTS0534827).

Monsanto Chemical Co. (1973). Letter from P. L. Wright to N. J. Hunt (April 4) (also cited in OTS0571679).

Data from these additional sources were not summarized because insufficient study information was available.

Izmerov, N. F. et al (1982). Toxicometric Parameters of Industrial Toxic Chemical Under Single Exposure, Centre of International Projects, GKNT, Moscow.

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom. Khim. Veschestv, 10:5-9 (CA71:47803v).

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom. Khim. Veschestv, 10:25-35.

Type: **Dermal Irritation**

Species/Strain: Rabbits/New Zealand White

Method: Young New Zealand White rabbits were used in the evaluation of the primary skin irritating properties of the test material. The test procedure was modeled after DOT (Department of Transportation) test conducted in accordance with 19 CFR, Chapter I, Sec. 173.40, as amended in Federal Register, Vol. 37, No. 57, March 23, 1972. Prior to the application of the test substance, the hair was clipped from the back and flanks of each rabbit. Two test sites located lateral to the midline of the back, approximately 10 cm apart were selected. One of the 2 sites was abraded by making 4 epidermal incisions, 2 perpendicular to the other 2, while the other test site remained intact. Exactly 0.5 mL of undiluted test substance was applied to each of the test sites on each rabbit. The test sites were immediately covered with gauze patches that were placed directly over the test sites and secured with tape. The trunk of each rabbit was then wrapped with plastic sheeting. The wrap held the patches in position and retarded evaporation of the test substance during the 4-hour exposure period. At the end of 4 hours, the plastic wrappings and patches were removed. The intact and abraded test sites were examined and scored separately for erythema and edema on a graded scale of 0 to 4. After 24 and 72 hours, the sites were again scored. In evaluating the average irritation present, the mean scores for erythema and edema of the intact test sites after 4, 24, and 72 hours were added. Similarly, the mean scores for erythema and edema of the abraded test sites after 4, 24, and 72 hours were added. These 2 values were totaled and divided by 6 to obtain the mean primary irritation score. The test substance

	was classified as corrosive if, when tested on intact rabbit skin, the structure of the tissue at the site of contact was destroyed or changed irreversibly after an exposure period of 4 hours or less.
GLP:	No
Test Substance:	Hexamethyleneimine, purity not specified
Results:	Hexamethyleneimine was classified as corrosive, with a mean primary irritation score of 8.0/8.0 (maximum primary irritation score of 8).
Reference:	The Celanese Chemical Co. (1972). Bio-Test IBT No. A1854 (cited in TSCA fiche OTS0520783, OTS0206028, OTS0534489).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Dermal Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 179-74.

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 180-74.

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-31, "Toxicological Investigation of CP 18407 – HMI Refined" (April 2) (cited in TSCA fiche OTS0539976).

Monsanto Chemical Co. (1973). Letter from P. L. Wright to N. J. Hunt (April 4) (also cited in OTS0571679).

Rohm and Haas (1985). Report No. 85R 0051 (cited in TSCA fiche OTS0540608).

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom. Khim. Veschestv, 10:25-35 (CA71:47804w).

Monsanto Chemical Co. (1972). Younger Laboratories, Inc. Project Number Y-72-114, "Toxicological Investigation of HMI Binary Solution" (June 2) (cited in TSCA fiche OTS0534842).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-33, "Toxicological Investigation of CP 61337 – HMI Azeotrope" (April 2) (cited in TSCA fiche OTS0534827).

Data from these additional sources were not summarized because insufficient study information was available.

Latypova, R. M. and F. G. Murzakaev (1976). Gig. Tr. Okhr. Zdorov'ya Rab.

Neft. Neftekhim. Prom-sti., 9:129-131 (CA90:17319; also cited in HSDB/562).

Bazarova, L. A. and N. I. Osipenko (1967). Toksikol. Novykh Prom. Khim. Veshchestv, 9:91-101 (CA70:27261).

Type: Dermal Sensitization (Mouse Ear Swelling Test – MEST)

Species/Strain:	Female mice/CF-1
Method:	Female mice were allowed to acclimate for 1 week after arrival in the laboratory, then were screened to remove any from testing that had ears that appeared red or swollen. Female mice, 6-8 weeks old, were shaved and tape stripped at the start of the study. As a standard part of this design, 2 intradermal injections, totaling 0.05 mL, of Freund's complete adjuvant emulsion (FCA) were performed into the stomach induction site of unanaesthetized mice prior to the 1st induction application. All mice were then topically dosed with 100 µL of the test substance in solvent (acetone) or solvent alone (control) applied to the center of the shaved region. The application was allowed to dry before the mouse was returned to its cage. Tape stripping and topical application of the appropriate solution to the stomach were repeated for 3 additional consecutive days. Seven days after the final topical application to the stomach, 20 µL of the test substance in solution was applied to the left ear of each mouse (test and control), and 20 µL of the solvent was applied to the right ear. At 24 and 48 hours after this challenge, mice were lightly anesthetized and the thickness of both ears was measured. As an additional guard against false positives, ear thickness may also have been measured on the day before challenge to protect against the small random chance of a naturally occurring "difference" in test or control groups. Hexamethyleneimine (1% in propylene glycol) was also evaluated by a patching induction method. To evaluate the effect of occlusive patching on the induction of a sensitization response, mice were shaved, tape stripped, injected intradermally with FCA, and patched. The test substance was applied to a small cotton swatch, which was then wrapped with tape. Only the cotton swatch was utilized. Unanaesthetized mice were wrapped for 24 hours every other day for 6 days, being tape stripped prior to each application.
GLP:	Unknown
Test Substance:	Hexamethyleneimine, purity = 98%
Results:	Hexamethyleneimine produced sensitization reactions in 40% of the mice using the mouse ear swelling test (MEST), but produced 0% response in the patching induction method.
Reference:	Gad, S. C. et al. (1986). Toxicol. Appl. Pharmacol., 84:93-114.

Reliability:	Medium because a suboptimal study design was used.

Additional References for Dermal Sensitization: None Found.

Type:	**Eye Irritation**
Species/Strain:	Male rabbits/New Zealand White
Method:	One day prior to dosing, the eyes of 6 male New Zealand White rabbits were examined grossly. Following gross examination fluorescein solution was placed onto the eye, the eye was flushed with water, and reexamined to determine any pre-existing ocular abnormalities. On the day of dosing, 0.1 mL of hexamethyleneimine (neat material) was applied to the corneal surface of the rabbits. The eyelids were held open momentarily after dosing and then released gently to allow the rabbit to blink freely. Approximately 10% of the applied test substance was blinked or fell from the treated eye, but the cornea and surrounding area were observed to be covered with the test substance. The treated eyes of 3 rabbits were irrigated with water for approximately 60 seconds beginning 20-30 seconds after dosing. The eyes of the other 3 rabbits remained unwashed. The treated eyes were scored according to the Draize procedure, and sodium fluorescein was used as an adjunct to gross examination of the eyes.
GLP:	Unknown
Test Substance:	Hexamethyleneimine (neat material), purity not specified
Results:	At 24 hours, the mean value for the cornea (calculated from 3 rabbits, unwashed eyes) was 80.0, and the conjunctive mean value was 19.0. All 6 rabbits exhibited blanching of the nictitating membrane and eschar on the eyelids. In addition, 3 of the rabbits had blanching of the conjunctiva, while the conjunctiva of the remaining rabbits was not visible due to the eschar on the eyelids. The iris of all rabbits was unscorable due to severity of the opacity. The study was terminated after the 24-hour observation and the rabbits were killed.
Reference:	Rohm and Haas (1985). Report No. 85R 0051 (cited in TSCA fiche OTS0540608).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Eye Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Monsanto Chemical Co. (1973). Letter from P. L. Wright to N. J. Hunt (April 4)

(also cited in OTS0571679).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-31, "Toxicological Investigation of CP 18407 – HMI Refined" (April 2) (cited in TSCA fiche OTS0539976).

Monsanto Chemical Co. (1972). Younger Laboratories, Inc. Project Number Y-72-114, "Toxicological Investigation of HMI Binary Solution" (June 2) (cited in TSCA fiche OTS0534842).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-33, "Toxicological Investigation of CP 61337 – HMI Azeotrope" (April 2) (cited in TSCA fiche OTS0534827).

5.2 Repeated Dose Toxicity

5.2.1 Repeated Dose Toxicity

Type:	**Combined Repeated Dose Toxicity and Reproductive/Developmental Toxicity Screen**
Species/Strain:	Wistar
Sex/Number:	40 males and 40 females
Exposure Period:	Twenty-eight (28) days (males); 38-56 days (females)
Frequency of Treatment:	Daily gavage
Exposure Levels:	0, 10, 25 and 50 mg/kg/day
Method:	OECD Method 422; Combined repeated dose toxicity study with reproduction/developmental toxicity screening test.

Dose level selection for the main study was based on a 5-day pilot gavage study using 3 rats/sex per group administered 50, 200 and 400/500 mg/kg/d HMI. As severe toxicity was observed in the 200 mg/kg/d group and higher, as evidenced by clinical signs, body weight loss, decreased liver and kidney weights, one rat sacrificed in a moribund state, and macroscopic and microscopic findings in the stomach and small intestine, 50 mg/kg/d was chosen as an adequate high dose for the main study.

Daily gavage doses, prepared in Milli-U water, were homogenized and delivered within 4 hr of preparation.

Animals were housed 5/group during premating, 1:1 (M:F) during mating, and individually thereafter. Mortality checks were made 2X/day and detailed clinical signs recorded daily. Individual adult (male and female) body weights and food consumption were recorded weekly; additionally, body weights were recorded on gestation days 0, 7, 14 and 21 and on lactation days 1 and 4 for all females. Water consumption was subjectively appraised.

Groups of 5 adult rats/sex/group were administered a Functional Observation Battery (FOB), including startle, reflex and motor activity testing; males were administered this examination during week 4 and females during the lactation period. Prior to autopsy, 5 rats/sex/group were evaluated for a full range of hematology (15 indices) and clinical blood biochemistry (14 indices) parameters. At necropsy, a thorough examination was made of the cranial, thoracic and abdominal tissue and organs (with special attention given to the reproductive organs) and all gross lesions were examined. Liver, kidney, testes, and epididymides weights were recorded for all animals at necropsy as well as the adrenals, brain, heart, spleen and thymus for 5 rats/sex/group. Microscopic examinations were completed on 14 tissues/organs (including all reproductive organs) for all rats at necropsy and an additional 24 tissues/organs selected from 5 rats/sex/group selected for subsequent examination.

GLP: Yes

Test Substance: Hexamethyleneimine; purity of 99.6%

Results: NOAEL Dose: >= 25 mg/kg-bw
LOAEL Dose: = 50 mg/kg-bw. Macroscopic glandular/forestomach mucosal thickening following gavage; upon microscopic examination, these tissues were considered normal.

Results Remarks: No treatment-related effects were observed on mortality, clinical signs, body weight, food consumption, functional observations, clinical laboratory investigations, organ weights, or microscopic examination. Analytical determination of dosing formulations indicated they were generally prepared accurately, were homogeneous and were stable for the dosing period.

Results of Reproductive/Developmental Toxicity parameters are reported in Robust Summary form in Section 5.4 of this dossier.

Reference: INVISTA S.á r.l. Internal Report. (2006). NOTOX B.V. Study no. 456727.

Reliability: High; Klimisch Code = 1; Reliable without restriction. Study conducted according to current testing guidelines, followed GLPs, and is well documented.

5.2.2 Repeated Dose Toxicity

Type: 2-Week Oral

Species/Strain: Rats/CFN

Sex/Number: Male/6 per dose level

Exposure Period: 2 weeks

Frequency of Treatment:	5 times/week
Exposure Levels:	0 (control), 90 mg/kg
Method:	The test substance was administered to rats (6/level) as a 1% aqueous solution 5 times/week for 2 weeks. Three rats were sacrificed 4 hours after the 10th treatment, and 3 rats were sacrificed 10 days after the 10th treatment. Gross pathology included 13 tissues/organs, and microscopic examination included 11 tissues/organs. Additionally, 7 organs/tissues were weighed.
GLP:	No
Test Substance:	Hexamethyleneimine, purity not specified
Results:	No mortality was observed. No clinical signs of toxicity, other than some temporary discomfort at dosing was observed in the rats treated with the test substance. No evidence of pathological change attributable to treatment was observed.
Reference:	DuPont Co. (1958). Unpublished Data, Haskell Laboratory Report No. 65-58.
Reliability:	Low because an inappropriate method or study design was used.

Additional Reference for Repeated Dose Toxicity:

Data from this additional source were not summarized because insufficient study information was available.

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom. Khim. Veschestv, 10:25-35 (CA71:47804w).

5.3 Developmental Toxicity: See information in Reproductive Toxicity Section.

5.4 Reproductive Toxicity

5.4.1 Type: Combined Repeated Dose Toxicity and Reproductive Toxicity Screen

Species/Strain:	Wistar
Sex/Number:	40 males and 40 females
Administration:	Gavage
Exposure Period:	Seven days a week
Frequency of Treatment:	Males – 14 days prior to mating, during mating and up to study termination on day 29. Females – 14-days prior to mating, during mating, gestation and to at least the third lactation day (total of 56 days).
Exposure Levels:	0, 10, 25 and 50 mg/kg/d HMI
Method:	OECD Method 422; Combined repeated dose toxicity study with reproduction/developmental toxicity screening test. Daily gavage doses, prepared in Milli-U water, were

homogenized and delivered (5 ml/Kg) within 4 hr of preparation. Dose levels were confirmed analytically. Groups of 10 male and 10 female rats were used for each study group. Each male rat was exposed for 2 wks prior to mating, during mating and up to termination on test day 29. Females were similarly dosed and dosing extended through gestation until after at least the third day of lactation (total up to 56 days). Animals were housed 5/group during premating, 1:1 (M:F) during mating, and individually once copulation was confirmed (observation of ejected copulation plug). Three females (1 LD and 2 MD) were separated from cohabitation with the first male after 10 days and introduced to another male until mating had occurred. All offspring remained with their respective dam. Mortality checks were made 2X/day and detailed clinical signs recorded daily.
Individual adult (male and female) body weights and food consumption were recorded weekly; additionally, body weights were recorded on gestation days 0, 7, 14 and 21 and on lactation days 1 and 4 for all females. Water consumption was subjectively appraised. Parental mating and fertility indices (paired partner, mating date, confirmation of pregnancy, delivery day) were recorded. At necropsy, special attention was given to the reproductive organs as a thorough examination was made of the cranial, thoracic and abdominal tissues and organs and all gross lesions. The number of implantation sites and corpora lutea for each adult female was also recorded. Testes and epididymides weights were recorded for each male rat from all test groups at necropsy. Microscopic examinations were completed on 14 tissues/organs for all rats at necropsy, including all reproductive organs. Females were allowed to litter normally and any deficiencies in maternal care noted. The following offspring parameters were evaluated for all test groups: number of live and dead pups on lactation day 1 and daily thereafter to study term; individual pup weights on days 1 and 4 of lactation, the sex of each pup and a thorough external examination at necropsy. Dunnet; Steel; Fisher; Student's T were statistical tools used.

GLP: Yes

Test Substance: Hexamethyleneimine, purity of 99.6%

Results: Parental NOAEL Dose:>= 50 mg/kg-bw
Parental NOAEL effect assessment: No treatment-related effects observed.
F1 NOAEL Dose:>= 50 mg/kg
F1 NOAEL effect assessment: No treatment-related effects observed.
Actual dosage received by dose level by sex: Target levels of 50, 25, and 10 mg/kg (analytically confirmed).

	Conclusion: Parental/F1 Data: No reproduction or breeding toxicity was observed in parental generation at highest dose (50 mg/kg) tested. Offspring Data: No developmental toxicity was observed in offspring at highest dosage (50 mg/kg) tested.
Reference:	INVISTA S.á r.l.. Internal report (2006). NOTOX B.V. Study no. 456727
Reliability:	High; Klimisch Code = 1; Reliable without restriction. Study conducted according to current testing guidelines, followed GLPs, and is well documented.

GENERAL

Remarks:	Results of Repeated Dose Toxicity parameters are reported in Robust Summary form in the Repeated Dose Toxicity section of this dossier.

5.4.2. Reproductive Toxicity

Species/Strain:	Rats/Sprague-Dawley
Sex/Number:	Male/Number not specified
Route of Administration:	*Hormone analysis:* Intraperitoneal injection *Sperm and testis morphology:* Subcutaneous implant
Exposure Period:	*Hormone analysis:* Single dose *Sperm and testis morphology:* 7 days
Frequency of Treatment:	*Hormone analysis:* Single dose *Sperm and testis morphology:* Daily
Exposure Levels:	*Hormone analysis:* 0, 10 mg/kg *Sperm and testis morphology:* 10 mg/kg
Method:	*Hormone analysis:* Male rats were administered a single dose of hexamethyleneimine in corn oil or corn oil alone. Rats were killed at 2, 6, or 24 hours. Blood was collected into lithium heparin syringes and centrifuged (1000 g for 15 minutes at 4ºC) to obtain plasma. Testes were removed and weighed, the capsules were pierced at the caudal pole, and the interstitial fluid was collected by draining over 18 hours at 4ºC. Interstitial fluid from paired testes was combined. Plasma and interstitial fluid were used immediately for testosterone determination. For hormone analyses conducted after collection, samples were stored overnight at -20ºC or for longer periods at -70ºC. *Sperm and testis morphology:* Male rats were surgically implanted subcutaneously with osmotic mini-pumps charged to deliver 10 mg/kg hexamethyleneimine, dissolved in PEG200, daily for 7 days. Rats were killed at 28 days after implantation, and the testes and cauda epididymis were removed. The distal cauda was chopped into culture medium and incubated for 15 minutes at 37ºC, with gentle medium and incubated for 15 minutes at 37ºC, with gentle swirling to evenly distribute the sperm. This sperm suspension was diluted into phosphate-buffered saline and

cooled over ice to kill the sperm prior to analysis. Testes were preserved in Bouin's fixative, embedded in wax, and processed through to hematoxylin- and eosin-stained sections (5 µm) for examination by light microscopy.

Samples of the sperm preparation were smeared onto microscope slides, allowed to dry, then fixed in acetone, and stained with a solution of 1% acetic acid containing trypan blue/naphthol yellow/eosin Y. The excess stain was removed by draining and the slides were rinsed twice in 1% acetic acid. After air drying, the slides were rinsed in xylene and cover slips were mounted. Each slide was scanned (40x magnification) and a minimum of 200 sperm were scored for tail (including mid-piece) and head abnormalities.

GLP: Unknown

Test Substance: Hexamethyleneimine, purity not specified

Results: The effect of hexamethyleneimine on testosterone biosynthesis was studied at concentrations that did not cause apparent systemic toxicity. No effects upon plasma or interstitial fluid concentrations were demonstrated with hexamethyleneimine at 10 mg/kg.

Administration of hexamethyleneimine at 10 mg/kg/day over a 7-day period from a subcutaneously implanted osmotic mini-pump failed to show any morphological changes in the testes. Hexamethyleneimine did not induce any abnormal changes in epididymal sperm morphology.

Reference: Ellis, M. K. et al. (1998). Toxicol. Appl. Pharmacol., 151:22-23.

Reliability: Medium because a suboptimal study design was used.

Additional References for Reproductive Toxicity: None Found.

5.5 Genetic Toxicity

Type: ***In vitro*** **Bacterial Reverse Mutation Test**

Tester Strains: *Salmonella typhimurium* TA97a, TA98, TA100, TA1535 *Escherichia coli* WP2 *uvr*A (pKM101)

Exogenous Metabolic Activation: Aroclor -induced rat liver S-9

Exposure Concentrations: 0, 10, 50, 100, 500, 1000, 2500, 5000 µg/plate

Method: The study consisted of a single trial that assessed test substance mutagenicity. Three replicates were plated for each tester strain in the presence and absence of the S-9 exogenous metabolic activation system at each concentration. Positive and negative controls were included for each strain and condition. The negative control was

sterile water, and the positive controls included 2-nitrofluorene, N-ethyl-N-nitro-N-nitroguanidine, sodium azide, ICR 191 acridine mutagen, 9,10-dimethyl-1,2-benzanthracene, and 2-aminoanthracene. Treatments in the presence of the exogenous metabolic activation system were conducted by adding 0.1 mL of negative or positive control or test substance solution, 0.5 mL of S-9 metabolic activation system, and 0.1 mL of an overnight culture containing approximately 1x10 bacteria to approximately 2 mL of top agar. These components were briefly mixed and poured onto a minimal glucose agar plate. Treatments in the absence of the exogenous S-9 metabolic activation system were the same as those in the presence of the exogenous metabolic activation system with the exception that 0.5 mL of sterile buffer was used as a replacement for the volume of the activation system. After pouring onto the surface of minimal glucose agar plates, the top agar was allowed time to solidify, and the individually labeled plates were inverted and incubated at 37^{o}C for approximately 48 hours. Plates were refrigerated at approximately 4^{o} C prior to evaluation and counting of revertant colonies.

Bacterial background lawns were evaluated for evidence of test substance toxicity and precipitation. Evidence of toxicity was scored relative to the concurrent negative control plates and recorded with the mean revertant count for the strain, condition, and concentration. Revertant colonies for a given tester strain and condition were counted by an automated colony counter unless the plate exhibited excessive toxicity.

A test substance was classified as positive (i.e., mutagenic) if the mean number of revertants in any strain at any test substance concentration was at least 2 times greater than the mean of the concurrent vehicle control and there was a concentration-related increase in the mean revertants per plate in that same strain. A test substance was classified as negative (i.e., not mutagenic) if there were no test substance concentrations with a mean number of revertants that were at concentrations with a mean number of revertants that were at least 2 times greater than the mean of concurrent vehicle control, or there was no concentration-related increase in the mean revertants per plate in that same strain.

GLP: Yes

Test Substance: Hexamethyleneimine, purity 99.5%

Results: Negative

Remarks: No precipitate was observed at any concentration in any of the *Salmonella* strains or in the *Escherichia coli* strain. Toxicity was observed through the reduction of the microcolony background lawns of all strains. This was

observed in all strains at concentrations =1000 µg/plate (non-activated test system), and at concentrations =2500 µg/plate (activated test system) in all strains except TA1535, where toxicity was observed only at the top dose of 5000 µg/plate. In addition, a concentration-related reduction in the mean number of revertant colonies per plate were observed in some strains. No test substance concentration reached a mean number of revertants that was 2 times greater than the mean of the concurrent vehicle control, and there was no concentration-related increase in the mean revertants per plate in any strain. The mean positive control value exhibited greater than a 3-fold increase over the respective negative control value for each tester strain.

Reference: DuPont Co. (1999). Unpublished Data, Haskell Laboratory Report No. DuPont-2754.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for *In vitro* Bacterial Reverse Mutation Test: None Found.

Type: ***In vitro*** **Chromosomal Aberration Assay in Peripheral Human Lymphocytes**

Strain or cell type or line: Human Lymphocytes

Metabolic Activation: Adult male Wistar rats; orally dosed for 3 days with 80 mg/kg Phenobarbital and 100 mg/kg ß-naphthoflavone in corn oil; livers harvested 24 h after last dose.

Concentrations Tested:
Experiment # 1 (3-h exposure; 24-h fixation)
a) With metabolic activation - 100, 333, 992 µg/mL
b) Without metabolic activation – 100, 332, 992 µg/mL
Experiment # 2 (24-h exposure; 24-h fixation; without metabolic activation):
= 100, 200, 300, 350, 400, 450, 500, 600 µg/mL.
(48-h exposure; 48-h fixation; without metabolic activation):
= 100, 300, 400, 500, 600, 650, 700 µg/mL.
(3-h exposure; 48-h fixation; with metabolic activation):
= 100, 333, 992 µg/mL.

Method:

Two independent experiments were conducted, as outlined above. Human lymphocytes obtained from a healthy male donor were cultured in RPMI 1640 medium, with blood, phytohemagglutinin, with or without metabolic activation system. pH (9.39) and osmolarity (290 mOsm/kg) were recorded at the highest test concentration. Culture conditions were maintained at 37±1^{o}C., carbon dioxide levels of 5.0±0.5%, and humidity ranging between 71-91%. Final test concentrations for experiment # 1 were chosen

based on the lack of toxicity observed up to 992 µg/mL in the Range-find study; further, no precipitate was observed at this level (992 µg/mL) either. Appropriate positive (those requiring and not requiring metabolic activation) and negative controls were included in the study design. Mitotic index was determined by counting the number of metaphases/1000 cells. Evaluation for chromosomal effects required scoring of cultures from at least 3 concentrations with the highest concentration producing a mitotic index (cytotoxicity) exceeding 50% and a low dose with a mitotic index similar to the solvent control. The number of aberrant cells and no. of aberrations were recorded for 100 metaphase chromosome spreads/culture and examined blind by light microscopy. Statistics were used for appropriate comparison using the Chi-square, one-sided test, $p<0.05$.

GLP: Yes.

Test Substance: Hexamethyleneimine; purity of 99.6%.

Results: Negative

Remarks: No clastogenic effect was observed either with or without metabolic activation when the test material was evaluated in two independent studies with varied exposure and fixation intervals up to a maximum level of 0.01 M concentration. Cytotoxicity was not observed during a 3-h exposure period, but was seen when Exposures of 24- and 48-h were employed.

Cytotoxic concentrations:

Experiment #1: No cytotoxicity (mitotic index expressed as % of untreated control value) was observed with or without metabolic activation:

µg/mL (without activation):	100*	333*	992*
Mitotic Index (%):	92	85	86
µg/mL (with activation):	100*	333*	992*
Mitotic Index (%):	116	121	119

Experiment #2: Cytotoxicity ranging between >50% and equal to untreated control values were observed in cultures without metabolic activation:

24-h exposure/24-h fixation:

µg/mL:	100	200*	300*	350*	400
Mitotic Index (%):	102	78	27	12	6

48-h exposure/48-h fixation:

µg/mL:	100*	300*	400*	500	550	600
Mitotic Index (%):	102	84	49	21	16	4

No affect on cytotoxicity was observed in cultures with metabolic activation in for 3-h exposure/48-h fixation period:

µg/mL:	100*	333*	992*
Mitotic Index (%):	106	109	121

	* Dosages investigated for chromosomal aberrations No statistically significant and/or biologically relevant increase in the number of cells with chromosomal aberrations was observed in either experiment, both in the presence and absence of a liver metabolic activation system. No effects were observed on the number of polyploid cells or cells with endoreduplicated chromosomes. Both positive and negative controls performed as expected.
Reference:	INVISTA S.á r.l. Internal Study (2006). NOTOX B.V. Project No. 456738
Reliability:	High; Study conducted according to current testing guidelines, followed GLPs, and is well documented. Klimisch Code = 1; Reliable without restriction.

Additional References for In vitro Mammalian Chromosomal Aberration Assay: None Found
Type: *In vivo* Genetic Toxicity Studies: No Data.